NovoLog®
insulin aspart (rDNA origin) injection

Questions and answers about using NovoLog®

What is NovoLog®?	NovoLog® (insulin aspart [rDNA origin] injection) is a fast-acting insulin analog from Novo Nordisk — a world leader in diabetes care. It is absorbed quickly and starts working within minutes to lower your blood sugar. This way, you may take your insulin and eat within 5 to 10 minutes, unlike the 30-minute wait required with regular human insulin.
What is NovoLog® FlexPen®?	NovoLog® FlexPen® is a discreet insulin pen that goes with you almost anywhere.* FlexPen® comes prefilled with NovoLog® and is ready to use in just a few steps. Please refer to the attached instructions for use. NovoLog® FlexPen® requires low injection force, making it easy to press. NovoLog® FlexPen® fits in a pocket or purse, so you'll have the insulin you need—right when you need it.†
Does my health insurance plan cover NovoLog® FlexPen®?	NovoLog® FlexPen® is available for the same co-pay as vial and syringe on most health insurance plans.
What type of needles should I use with NovoLog® FlexPen®?	NovoFine® disposable needles† are recommended. NovoFine® needles are very thin and short.
How do I save money on NovoLog® FlexPen®?	Regardless of your health insurance plan, you can save up to $50 off your first FlexPen® prescription and up to $25 off your next three prescriptions for a total savings of up to $125‡ with the Novo Nordisk Savings Card. Learn more about this offer from your health care provider or by visiting MyFlexPen.com.
How do I get NovoLog® FlexPen®?	NovoLog® FlexPen® is only available with a prescription. Ask your health care provider today if NovoLog® FlexPen® is right for you. Find out more about the benefits of FlexPen® at MyFlexPen.com or call 1-800-727-6500.

Indications and Usage

What is NovoLog® (insulin aspart [rDNA origin] injection)?

- NovoLog® is a man-made insulin used to control high blood sugar in adults and children with diabetes mellitus.

Important Safety Information

Who should not use NovoLog®?

- Do not use NovoLog® if your blood sugar is too low (hypoglycemia) or you are allergic to any of its ingredients.

Please see additional Important Safety Information on the next page and accompanying Patient Information.

*If NovoLog® FlexPen® is kept at room temperature below 86° F for up to 28 days.

† Needles are sold separately and may require a prescription in some states. Needles and FlexPen® must not be shared. Refer to the user manual for information on assembly and injection.

‡ Eligible patients only. Discount is not to exceed patient's out-of-pocket expenses. Please read terms & conditions for eligibility requirements at MyFlexPen.com.

Important Safety Information (continued)

What should I tell my healthcare provider before taking NovoLog® (insulin aspart [rDNA origin] injection)?

- About all of your medical conditions, including liver or kidney problems.
- If you are pregnant, breastfeeding, or plan to do either.
- About all prescription and nonprescription medicines you take, including supplements, as your dose may need to change.

How should I take NovoLog®?

- Eat a meal within 5 to 10 minutes after using NovoLog® (insulin aspart [rDNA origin] injection), a fast-acting insulin, to avoid low blood sugar. Do not inject NovoLog® if you do not plan to eat right after your injection or bolus pump infusion.
- Do not mix NovoLog® with any other insulin when used in a pump or with any insulin other than NPH when used with injections by syringe.
- Do not change your dose or type of insulin unless you are told to by your healthcare provider.
- Do not share needles, insulin pens, or syringes.
- Check your blood sugar levels as directed by your healthcare provider.

What should I consider while using NovoLog®?

- Alcohol, including beer and wine, may affect your blood sugar.
- Be careful when driving a car or operating machinery. You may have difficulty concentrating or reacting if you have low blood sugar. Talk to your healthcare provider if you often have low blood sugar or no warning signs of low blood sugar.

What are the possible side effects of NovoLog®?

- Low blood sugar, including when too much is taken. Some symptoms include sweating, shakiness, confusion, and headache. Severe low blood sugar can cause unconsciousness, seizures, and death.
- Serious allergic reactions may occur. Get medical help right away, if you develop a rash over your whole body, have trouble breathing, a fast heartbeat, or sweating.
- Other side effects include injection site reactions (like redness, swelling, and itching), skin thickening or pits at the injection site, swelling of your hands and feet, vision changes, low potassium in your blood, and weight gain.

Please see accompanying Patient Information.

Talk to your doctor about the importance of diet and exercise in your treatment plan.

You can get additional help with your diabetes care at Cornerstones4Care.com.

Partnership for Prescription Assistance

If you need assistance with prescription drug costs, help may be available.
Visit pparx.org or call 1-888-4PPA-NOW.

You are encouraged to report negative side effects of prescription drugs to the FDA.
Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

novo nordisk®

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NovoLog®
insulin aspart (rDNA origin) injection

NovoLog®

insulin aspart (rDNA origin) injection

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NovoLog® safely and effectively. See full prescribing information for NovoLog®.

NovoLog® (insulin aspart [rDNA origin] injection) solution for subcutaneous use

Initial U.S. Approval: 2000

RECENT MAJOR CHANGES

- Dosage and Administration (2.3) 7/2009
- Warnings and Precautions, Administration (5.1) 10/2009

INDICATIONS AND USAGE

- NovoLog® is an insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus (1.1).

DOSAGE AND ADMINISTRATION

- The dosage of NovoLog® must be individualized.
- *Subcutaneous injection:* NovoLog® should generally be given immediately (within 5-10 minutes) prior to the start of a meal (2.2).
- *Use in pumps:* Change the NovoLog® in the reservoir at least every 6 days, change the infusion set, and the infusion set insertion site at least every 3 days. NovoLog® should not be mixed with other insulins or with a diluent when it is used in the pump (2.3).
- *Intravenous use:* NovoLog® should be used at concentrations from 0.05 U/mL to 1.0 U/mL insulin aspart in infusion systems using polypropylene infusion bags. NovoLog® has been shown to be stable in infusion fluids such as 0.9% sodium chloride (2.4).

DOSAGE FORMS AND STRENGTHS

Each presentation contains 100 Units of insulin aspart per mL (U-100)

- 10 mL vials (3)
- 3 mL PenFill® cartridges for the 3 mL PenFill® cartridge device (3)
- 3 mL NovoLog® FlexPen® (3)

CONTRAINDICATIONS

- Do not use during episodes of hypoglycemia (4).
- Do not use in patients with hypersensitivity to NovoLog® or one of its excipients.

WARNINGS AND PRECAUTIONS

- Hypoglycemia is the most common adverse effect of insulin therapy. Glucose monitoring is recommended for all patients with diabetes. Any change of insulin dose should be made cautiously and only under medical supervision (5.1, 5.2).
- Insulin, particularly when given intravenously or in settings of poor glycemic control, can cause hypokalemia. Use caution in patients predisposed to hypokalemia (5.3).
- Like all insulins, NovoLog® requirements may be reduced in patients with renal impairment or hepatic impairment (5.4, 5.5).
- Severe, life-threatening, generalized allergy, including anaphylaxis, may occur with insulin products, including NovoLog® (5.6).

ADVERSE REACTIONS

Adverse reactions observed with NovoLog® include hypoglycemia, allergic reactions, local injection site reactions, lipodystrophy, rash and pruritus (6).

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk Inc. at 1-800-727-6500 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- The following may increase the blood-glucose-lowering effect and susceptibility to hypoglycemia: oral antidiabetic products, pramlintide, ACE inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, propoxyphene, salicylates, somatostatin analogs, sulfonamide antibiotics (7).
- The following may reduce the blood-glucose-lowering effect: corticosteroids, niacin, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, salbutamol, terbutaline), isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (e.g., in oral contraceptives), atypical antipsychotics (7).
- Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin (7).
- Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia (7).
- The signs of hypoglycemia may be reduced or absent in patients taking sympatholytic products such as beta-blockers, clonidine, guanethidine, and reserpine (7).

USE IN SPECIFIC POPULATIONS

- Pediatric: Has not been studied in children with type 2 diabetes. Has not been studied in children with type 1 diabetes <2 years of age (8.4).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 6/2011

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Treatment of Diabetes Mellitus

NovoLog® is an insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing

NovoLog® is an insulin analog with an earlier onset of action than regular human insulin. The dosage of NovoLog® must be individualized. NovoLog® given by subcutaneous injection should generally be used in regimens with an intermediate or long-acting insulin [*see Warnings and Precautions (5), How Supplied/Storage and Handling (16.2)*]. The total daily insulin requirement may vary and is usually between 0.5 to 1.0 units/kg/day. When used in a meal-related subcutaneous injection treatment regimen, 50 to 70% of total insulin requirements may be provided by NovoLog® and the remainder provided by an intermediate-acting or long-acting insulin. Because of NovoLog®'s comparatively rapid onset and short duration of glucose lowering activity, some patients may require more basal insulin and more total insulin to prevent pre-meal hyperglycemia when using NovoLog® than when using human regular insulin.

Do not use NovoLog® that is viscous (thickened) or cloudy; use only if it is clear and colorless. NovoLog® should not be used after the printed expiration date.

2.2 Subcutaneous Injection

NovoLog® should be administered by subcutaneous injection in the abdominal region, buttocks, thigh, or upper arm. Because NovoLog® has a more rapid onset and a shorter duration of activity than human regular insulin, it should be injected immediately (within 5-10 minutes) before a meal. Injection sites should be rotated within the same region to reduce the risk of lipodystrophy. As with all insulins, the duration of action of NovoLog® will vary according to the dose, injection site, blood flow, temperature, and level of physical activity.

NovoLog® may be diluted with Insulin Diluting Medium for NovoLog® for subcutaneous injection. Diluting one part NovoLog® to nine parts diluent will yield a concentration one-tenth that of NovoLog® (equivalent to U-10). Diluting one part NovoLog® to one part diluent will yield a concentration one-half that of NovoLog® (equivalent to U-50).

2.3 Continuous Subcutaneous Insulin Infusion (CSII) by External Pump

NovoLog® can also be infused subcutaneously by an external insulin pump [*see Warnings and Precautions (5.8, 5.9), How Supplied/Storage and Handling (16.2)*]. Diluted insulin should not be used in external insulin pumps. Because NovoLog® has a more rapid onset and a shorter duration of activity than human regular insulin, pre-meal boluses of NovoLog® should be infused immediately (within 5-10 minutes) before a meal. Infusion sites should be rotated within the same region to reduce the risk of lipodystrophy. The initial programming of the external insulin infusion pump should be based on the total daily insulin dose of the previous regimen. Although there is significant interpatient variability, approximately 50% of the total dose is usually given as meal-related boluses of NovoLog® and the remainder is given as a basal infusion. **Change the NovoLog® in the reservoir at least every 6 days, change the infusion sets and the infusion set insertion site at least every 3 days.**

The following insulin pumps† have been used in NovoLog® clinical or *in vitro* studies conducted by Novo Nordisk, the manufacturer of NovoLog®:

- Medtronic Paradigm® 512 and 712
- MiniMed 508
- Disetronic® D-TRON® and H-TRON®

Before using a different insulin pump with NovoLog®, read the pump label to make sure the pump has been evaluated with NovoLog®.

2.4 Intravenous Use

NovoLog® can be administered intravenously under medical supervision for glycemic control with close monitoring of blood glucose and potassium levels to avoid hypoglycemia and hypokalemia [*see Warnings and Precautions (5), How Supplied/Storage and Handling (16.2)*]. For intravenous use, NovoLog® should be used at concentrations from 0.05 U/mL to 1.0 U/mL insulin aspart in infusion systems using polypropylene infusion bags. NovoLog® has been shown to be stable in infusion fluids such as 0.9% sodium chloride.

Inspect NovoLog® for particulate matter and discoloration prior to parenteral administration.

3 DOSAGE FORMS AND STRENGTHS

NovoLog® is available in the following package sizes: each presentation contains 100 units of insulin aspart per mL (U-100).

- 10 mL vials
- 3 mL PenFill cartridges for the 3 mL PenFill® cartridge delivery device (with or without the addition of a NovoPen® 3 PenMate®) with NovoFine® disposable needles
- 3 mL NovoLog® FlexPen®

4 CONTRAINDICATIONS

NovoLog® is contraindicated

- during episodes of hypoglycemia
- in patients with hypersensitivity to NovoLog® or one of its excipients.

5 WARNINGS AND PRECAUTIONS

5.1 Administration

NovoLog® has a more rapid onset of action and a shorter duration of activity than regular human insulin. An injection of NovoLog® should immediately be followed by a meal within 5-10 minutes. Because of NovoLog®'s short duration of action, a longer acting insulin should also be used in patients with type 1 diabetes and may also be needed in patients with type 2 diabetes. Glucose monitoring is recommended for all patients with diabetes and is particularly important for patients using external pump infusion therapy.

Any change of insulin dose should be made cautiously and only under medical supervision. Changing from one insulin product to another or changing the insulin strength may result in the need for a change in dosage. As with all insulin preparations, the time course of NovoLog® action may vary in different individuals or at different times in the same individual and is dependent on many conditions, including the site of injection, local blood supply, temperature, and physical activity. Patients who change their level of physical activity or meal plan may require adjustment of insulin dosages. Insulin requirements may be altered during illness, emotional disturbances, or other stresses.

Patients using continuous subcutaneous insulin infusion pump therapy must be trained to administer insulin by injection and have alternate insulin therapy available in case of pump failure.

I Needles and NovoLog® FlexPen® must not be shared.

5.2 Hypoglycemia

Hypoglycemia is the most common adverse effect of all insulin therapies, including NovoLog®. Severe hypoglycemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or death. Severe hypoglycemia requiring the assistance of another person and/or parenteral glucose infusion or glucagon administration has been observed in clinical trials with insulin, including trials with NovoLog®.

The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulations [*see Clinical Pharmacology (12)*]. Other factors such as changes in food intake (e.g., amount of food or timing of meals), injection site, exercise, and concomitant medications may also alter the risk of hypoglycemia [*see Drug Interactions (7)*]. As with all insulins, use caution in patients with hypoglycemia unawareness and in patients who may be predisposed to hypoglycemia (e.g., patients who are fasting or have erratic food intake). The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. This may present a risk in situations where these abilities are especially important, such as driving or operating other machinery.

Rapid changes in serum glucose levels may induce symptoms of hypoglycemia in persons with diabetes, regardless of the glucose value. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as longstanding diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control [*see Drug Interactions (7)*]. These situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to the patient's awareness of hypoglycemia. Intravenously administered insulin has a more rapid onset of action than subcutaneously administered insulin, requiring more close monitoring for hypoglycemia.

5.3 Hypokalemia

All insulin products, including NovoLog®, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia that, if left untreated, may cause respiratory paralysis, ventricular arrhythmia, and death. Use caution in patients who may be at risk for hypokalemia (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations, and patients receiving intravenously administered insulin).

5.4 Renal Impairment

As with other insulins, the dose requirements for NovoLog® may be reduced in patients with renal impairment [*see Clinical Pharmacology (12.3)*].

5.5 Hepatic Impairment

As with other insulins, the dose requirements for NovoLog® may be reduced in patients with hepatic impairment [*see Clinical Pharmacology (12.3)*].

5.6 Hypersensitivity and Allergic Reactions

Local Reactions - As with other insulin therapy, patients may experience redness, swelling, or itching at the site of NovoLog® injection. These reactions usually resolve in a few days to a few weeks, but in some occasions, may require discontinuation of NovoLog®. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique. Localized reactions and generalized myalgias have been reported with injected metacresol, which is an excipient in NovoLog®.

Systemic Reactions - Severe, life-threatening, generalized allergy, including anaphylaxis, may occur with any insulin product, including NovoLog®. Anaphylactic reactions with NovoLog® have been reported post-approval. Generalized allergy to insulin may also cause whole body rash (including pruritus), dyspnea, wheezing, hypotension, tachycardia, or diaphoresis. In controlled clinical trials, allergic reactions were reported in 3 of 735 patients (0.4%) treated with regular human insulin and 10 of 1394 patients (0.7%) treated with NovoLog®. In controlled and uncontrolled clinical trials, 3 of 2341 (0.1%) NovoLog®-treated patients discontinued due to allergic reactions.

5.7 Antibody Production

Increases in anti-insulin antibody titers that react with both human insulin and insulin aspart have been observed in patients treated with NovoLog®. Increases in anti-insulin antibodies are observed more frequently with NovoLog® than with regular human insulin. Data from a 12-month controlled trial in patients with type 1 diabetes suggest that the increase in these antibodies is transient, and the differences in antibody levels between the regular human insulin and insulin aspart treatment groups observed at 3 and 6 months were no longer evident at 12 months. The clinical significance of these antibodies is not known. These antibodies do not appear to cause deterioration in glycemic control or necessitate increases in insulin dose.

5.8 Mixing of Insulins

- Mixing NovoLog® with NPH human insulin immediately before injection attenuates the peak concentration of NovoLog®, without significantly affecting the time to peak concentration or total bioavailability of NovoLog®. If NovoLog® is mixed with NPH human insulin, NovoLog® should be drawn into the syringe first, and the mixture should be injected immediately after mixing.
- The efficacy and safety of mixing NovoLog® with insulin preparations produced by other manufacturers have not been studied.
- Insulin mixtures should not be administered intravenously.

5.9 Continuous Subcutaneous Insulin Infusion by External Pump

When used in an external subcutaneous insulin infusion pump, NovoLog® should not be mixed with any other insulin or diluent. When using NovoLog® in an external insulin pump, the NovoLog®-specific information should be followed (e.g., in-use time, frequency of changing infusion sets) because NovoLog®-specific information may differ from general pump manual instructions.

Pump or infusion set malfunctions or insulin degradation can lead to a rapid onset of hyperglycemia and ketosis because of the small subcutaneous depot of insulin. This is especially pertinent for rapid-acting insulin analogs that are more rapidly absorbed through skin and have a shorter duration of action. Prompt identification and correction of the cause of hyperglycemia or ketosis is necessary. Interim therapy with subcutaneous injection may be required [*see Dosage and Administration (2.3), Warnings and Precautions (5.8, 5.9), How Supplied/Storage and Handling (16.2), and Patient Counseling Information (17.2)*].

NovoLog® should not be exposed to temperatures greater than 37°C (98.6°F). **NovoLog® that will be used in a pump should not be mixed with other insulin or with a diluent** [*see Dosage and Administration (2.3), Warnings and Precautions (5.8, 5.9), How Supplied/Storage and Handling (16.2), and Patient Counseling Information (17.2)*].

6 ADVERSE REACTIONS

Clinical Trial Experience

Because clinical trials are conducted under widely varying designs, the adverse reaction rates reported in one clinical trial may not be easily compared to those rates reported in another clinical trial, and may not reflect the rates actually observed in clinical practice.

- *Hypoglycemia*

  Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including NovoLog® [*see Warnings and Precautions (5)*].
- *Insulin initiation and glucose control intensification*

  Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy.
- *Lipodystrophy*

  Long-term use of insulin, including NovoLog®, can cause lipodystrophy at the site of repeated insulin injections or infusion. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue) and lipoatrophy (thinning of adipose tissue), and may affect insulin absorption. Rotate insulin injection or infusion sites within the same region to reduce the risk of lipodystrophy.
- *Weight gain*

  Weight gain can occur with some insulin therapies, including NovoLog®, and has been attributed to the anabolic effects of insulin and the decrease in glucosuria.
- *Peripheral Edema*

  Insulin may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.
- *Frequencies of adverse drug reactions*

  The frequencies of adverse drug reactions during NovoLog® clinical trials in patients with type 1 diabetes mellitus and type 2 diabetes mellitus are listed in the tables below.

Table 1: Treatment-Emergent Adverse Events in Patients with Type 1 Diabetes Mellitus (Adverse events with frequency ≥ 5% and occurring more frequently with NovoLog® compared to human regular insulin are listed)

	NovoLog® + NPH N= 596		Human Regular Insulin + NPH N= 286	
Preferred Term	**N**	**(%)**	**N**	**(%)**
Hypoglycemia*	448	75%	205	72%
Headache	70	12%	28	10%
Injury accidental	65	11%	29	10%
Nausea	43	7%	13	5%
Diarrhea	28	5%	9	3%

*Hypoglycemia is defined as an episode of blood glucose concentration <45 mg/dL, with or without symptoms. See Section 14 for the incidence of serious hypoglycemia in the individual clinical trials.

Table 2: Treatment-Emergent Adverse Events in Patients with Type 2 Diabetes Mellitus (except for hypoglycemia, adverse events with frequency ≥ 5% and occurring more frequently with NovoLog® compared to human regular insulin are listed)

	NovoLog® + NPH N= 91		Human Regular Insulin + NPH N= 91	
	N	**(%)**	**N**	**(%)**
Hypoglycemia*	25	27%	33	36%
Hyporeflexia	10	11%	6	7%
Onychomycosis	9	10%	5	5%
Sensory disturbance	8	9%	6	7%
Urinary tract infection	7	8%	6	7%
Chest pain	5	5%	3	3%
Headache	5	5%	3	3%
Skin disorder	5	5%	2	2%
Abdominal pain	5	5%	1	1%
Sinusitis	5	5%	1	1%

*Hypoglycemia is defined as an episode of blood glucose concentration <45 mg/dL, with or without symptoms. See Section 14 for the incidence of serious hypoglycemia in the individual clinical trials.

Postmarketing Data

The following additional adverse reactions have been identified during postapproval use of NovoLog®. Because these adverse reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency. Medication errors in which other insulins have been accidentally substituted for NovoLog® have been identified during postapproval use [*see Patient Counseling Information (17)*].

7 DRUG INTERACTIONS

A number of substances affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring.

- The following are examples of substances that may increase the blood-glucose-lowering effect and susceptibility to hypoglycemia: oral antidiabetic products, pramlintide, ACE inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, propoxyphene, salicylates, somatostatin analog (e.g., octreotide), sulfonamide antibiotics.
- The following are examples of substances that may reduce the blood-glucose-lowering effect: corticosteroids, niacin, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, salbutamol, terbutaline), isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (e.g., in oral contraceptives), atypical antipsychotics.
- Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin.
- Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.
- The signs of hypoglycemia may be reduced or absent in patients taking sympatholytic products such as beta-blockers, clonidine, guanethidine, and reserpine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B. All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. This background risk is increased in pregnancies complicated by hyperglycemia and may be decreased with good metabolic control. It is essential for patients with diabetes or history of gestational diabetes to maintain good metabolic control before

conception and throughout pregnancy. Insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in these patients. Therefore, female patients should be advised to tell their physician if they intend to become, or if they become pregnant while taking NovoLog®.

An open-label, randomized study compared the safety and efficacy of NovoLog® (n=157) versus regular human insulin (n=165) in 322 pregnant women with type 1 diabetes. Two-thirds of the enrolled patients were already pregnant when they entered the study. Because only one-third of the patients enrolled before conception, the study was not large enough to evaluate the risk of congenital malformations. Both groups achieved a mean HbA_{1c} of ~ 6% during pregnancy, and there was no significant difference in the incidence of maternal hypoglycemia.

Subcutaneous reproduction and teratology studies have been performed with NovoLog® and regular human insulin in rats and rabbits. In these studies, NovoLog® was given to female rats before mating, during mating, and throughout pregnancy, and to rabbits during organogenesis. The effects of NovoLog® did not differ from those observed with subcutaneous regular human insulin. NovoLog®, like human insulin, caused pre- and post-implantation losses and visceral/skeletal abnormalities in rats at a dose of 200 U/kg/day (approximately 32 times the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area) and in rabbits at a dose of 10 U/kg/day (approximately three times the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area). The effects are probably secondary to maternal hypoglycemia at high doses. No significant effects were observed in rats at a dose of 50 U/kg/day and in rabbits at a dose of 3 U/kg/day. These doses are approximately 8 times the human subcutaneous dose of 1.0 U/kg/day for rats and equal to the human subcutaneous dose of 1.0 U/kg/day for rabbits, based on U/body surface area.

8.3 Nursing Mothers

It is unknown whether insulin aspart is excreted in human milk. Use of NovoLog® is compatible with breastfeeding, but women with diabetes who are lactating may require adjustments of their insulin doses.

8.4 Pediatric Use

NovoLog® is approved for use in children for subcutaneous daily injections and for subcutaneous continuous infusion by external insulin pump. NovoLog® has not been studied in pediatric patients younger than 2 years of age. NovoLog® has not been studied in pediatric patients with type 2 diabetes. Please see *Section 14* ***CLINICAL STUDIES*** for summaries of clinical studies.

8.5 Geriatric Use

Of the total number of patients (n= 1,375) treated with NovoLog® in 3 controlled clinical studies, 2.6% (n=36) were 65 years of age or over. One-half of these patients had type 1 diabetes (18/1285) and the other half had type 2 diabetes (18/90). The HbA_{1c} response to NovoLog®, as compared to human insulin, did not differ by age, particularly in patients with type 2 diabetes. Additional studies in larger populations of patients 65 years of age or over are needed to permit conclusions regarding the safety of NovoLog® in elderly compared to younger patients. Pharmacokinetic/pharmacodynamic studies to assess the effect of age on the onset of NovoLog® action have not been performed.

10 OVERDOSAGE

Excess insulin administration may cause hypoglycemia and, particularly when given intravenously, hypokalemia. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise, may be needed. More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery. Hypokalemia must be corrected appropriately.

11 DESCRIPTION

NovoLog® (insulin aspart [rDNA origin] injection) is a rapid-acting human insulin analog used to lower blood glucose. NovoLog® is homologous with regular human insulin with the exception of a single substitution of the amino acid proline by aspartic acid in position B28, and is produced by recombinant DNA technology utilizing *Saccharomyces cerevisiae* (baker's yeast). Insulin aspart has the empirical formula $C_{256}H_{381}N_{65}O_{79}S_6$ and a molecular weight of 5825.8.

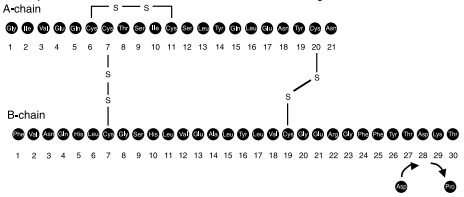


Figure 1. Structural formula of insulin aspart.

NovoLog® is a sterile, aqueous, clear, and colorless solution, that contains insulin aspart 100 Units/mL, glycerin 16 mg/mL, phenol 1.50 mg/mL, metacresol 1.72 mg/mL, zinc 19.6 mcg/mL, disodium hydrogen phosphate dihydrate 1.25 mg/mL, sodium chloride 0.58 mg/mL and water for injection. NovoLog® has a pH of 7.2-7.6. Hydrochloric acid 10% and/or sodium hydroxide 10% may be added to adjust pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The primary activity of NovoLog® is the regulation of glucose metabolism. Insulins, including NovoLog®, bind to the insulin receptors on muscle and fat cells and lower blood glucose by facilitating the cellular uptake of glucose and simultaneously inhibiting the output of glucose from the liver.

12.2 Pharmacodynamics

Studies in normal volunteers and patients with diabetes demonstrated that subcutaneous administration of NovoLog® has a more rapid onset of action than regular human insulin.

In a study in patients with type 1 diabetes (n=22), the maximum glucose-lowering effect of NovoLog® occurred between 1 and 3 hours after subcutaneous injection (see Figure 2). The duration of action for NovoLog® is 3 to 5 hours. The time course of action of insulin and insulin analogs such as NovoLog® may vary considerably in different individuals or within the same individual. The parameters of NovoLog® activity (time of onset, peak time and duration) as designated in Figure 2 should be considered only as general guidelines. The rate of insulin absorption and onset of activity is affected by the site of injection, exercise, and other variables [*see Warnings and Precautions (5.1)*].

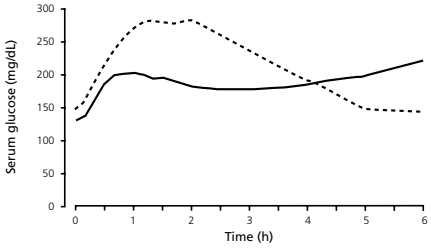
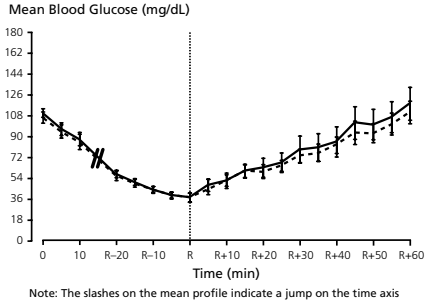


Figure 2. Serial mean serum glucose collected up to 6 hours following a single pre-meal dose of NovoLog® (solid curve) or regular human insulin (hatched curve) injected immediately before a meal in 22 patients with type 1 diabetes.

A double-blind, randomized, two-way cross-over study in 16 patients with type 1 diabetes demonstrated that intravenous infusion of NovoLog® resulted in a blood glucose profile that was similar to that after intravenous infusion with regular human insulin. NovoLog® or human insulin was infused until the patient's blood glucose decreased to 36 mg/dL, or until the patient demonstrated signs of hypoglycemia (rise in heart rate and onset of sweating), defined as the time of autonomic reaction (R) (see Figure 3).



Note: The slashes on the mean profile indicate a jump on the time axis

Figure 3. Mean blood glucose profiles following intravenous infusion of NovoLog® (hatched curve) and regular human insulin (solid curve) in 16 patients with type 1 diabetes. R represents the time of autonomic reaction.

12.3 Pharmacokinetics

The single substitution of the amino acid proline with aspartic acid at position B28 in NovoLog® reduces the molecule's tendency to form hexamers as observed with regular human insulin. NovoLog® is, therefore, more rapidly absorbed after subcutaneous injection compared to regular human insulin.

In a randomized, double-blind, crossover study 17 healthy Caucasian male subjects between 18 and 40 years of age received an intravenous infusion of either NovoLog® or regular human insulin at 1.5 mU/kg/min for 120 minutes. The mean insulin clearance was similar for the two groups with mean values of 1.2 l/h/kg for the NovoLog® group and 1.2 l/h/kg for the regular human insulin group.

Bioavailability and Absorption - NovoLog® has a faster absorption, a faster onset of action, and a shorter duration of action than regular human insulin after subcutaneous injection (see Figure 2 and Figure 4). The relative bioavailability of NovoLog® compared to regular human insulin indicates that the two insulins are absorbed to a similar extent.

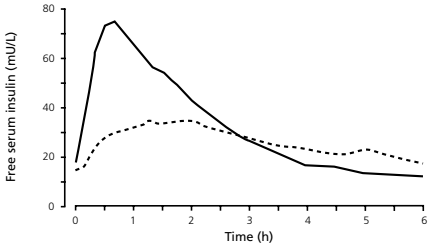


Figure 4. Serial mean serum free insulin concentration collected up to 6 hours following a single pre-meal dose of NovoLog® (solid curve) or regular human insulin (hatched curve) injected immediately before a meal in 22 patients with type 1 diabetes.

In studies in healthy volunteers (total n=107) and patients with type 1 diabetes (total n=40), NovoLog® consistently reached peak serum concentrations approximately twice as fast as regular human insulin. The median time to maximum concentration in these trials was 40 to 50 minutes for NovoLog® versus 80 to 120 minutes for regular human insulin. In a clinical trial in patients with type 1 diabetes, NovoLog® and regular human insulin, both administered subcutaneously at a dose of 0.15 U/kg body weight, reached mean maximum concentrations of 82 and 36 mU/L, respectively. Pharmacokinetic/pharmacodynamic characteristics of insulin aspart have not been established in patients with type 2 diabetes.

The intra-individual variability in time to maximum serum insulin concentration for healthy male volunteers was significantly less for NovoLog® than for regular human insulin. The clinical significance of this observation has not been established.

In a clinical study in healthy non-obese subjects, the pharmacokinetic differences between NovoLog® and regular human insulin described above, were observed independent of the site of injection (abdomen, thigh, or upper arm).

Distribution and Elimination - NovoLog® has low binding to plasma proteins (<10%), similar to that seen with regular human insulin. After subcutaneous administration in normal male volunteers (n=24), NovoLog® was more rapidly eliminated than regular human insulin with an average apparent half-life of 81 minutes compared to 141 minutes for regular human insulin.

Specific Populations

Children and Adolescents - The pharmacokinetic and pharmacodynamic properties of NovoLog® and regular human insulin were evaluated in a single dose study in 18 children (6-12 years, n=9) and adolescents (13-17 years [Tanner grade ≥ 2], n=9) with type 1 diabetes. The relative differences in pharmacokinetics and pharmacodynamics in children and adolescents with type 1 diabetes between NovoLog® and regular human insulin were similar to those in healthy adult subjects and adults with type 1 diabetes.

Gender - In healthy volunteers, no difference in insulin aspart levels was seen between men and women when body weight differences were taken into account. There was no significant difference in efficacy noted (as assessed by HbA_{1c}) between genders in a trial in patients with type 1 diabetes.

Obesity - A single subcutaneous dose of 0.1 U/kg NovoLog® was administered in a study of 23 patients with type 1 diabetes and a wide range of body mass index (BMI, 22-39 kg/m^2). The pharmacokinetic parameters, AUC and C_{max}, of NovoLog® were generally unaffected by BMI in the different groups – BMI 19-23 kg/m^2 (N=4); BMI 23-27 kg/m^2 (N=7); BMI 27-32 kg/m^2 (N=6) and BMI >32 kg/m^2 (N=6). Clearance of NovoLog® was reduced by 28% in patients with BMI >32 kg/m^2 compared to patients with BMI <23 kg/m^2.

Renal Impairment - Some studies with human insulin have shown increased circulating levels of insulin in patients with renal failure. A single subcutaneous dose of 0.08 U/kg NovoLog® was administered in a study to subjects with either normal (N=6) creatinine clearance (CLcr) (>80 ml/min) or mild (N=7; CLcr = 50-80 ml/min), moderate (N=3; CLcr = 30-50 ml/min) or severe (but not requiring hemodialysis) (N=2; CLcr = <30 ml/min) renal impairment. In this small study, there was no apparent effect of creatinine clearance values on AUC and C_{max} of NovoLog®. Careful glucose monitoring and dose adjustments of insulin, including NovoLog®, may be necessary in patients with renal dysfunction [*see Warnings and Precautions (5.4)*].

Hepatic Impairment - Some studies with human insulin have shown increased circulating levels of insulin in patients with liver failure. A single subcutaneous dose of 0.06 U/kg NovoLog® was administered in an open-label, single-dose study of 24 subjects (N=6/group) with different degree of hepatic impairment (mild, moderate and severe) having Child-Pugh Scores ranging from 0 (healthy volunteers) to 12 (severe hepatic impairment). In this small study, there was no correlation between the degree of hepatic failure and any NovoLog® pharmacokinetic parameter. Careful glucose monitoring and dose adjustments of insulin, including NovoLog®, may be necessary in patients with hepatic dysfunction [*see Warnings and Precautions (5.5)*].

The effect of age, ethnic origin, pregnancy and smoking on the pharmacokinetics and pharmacodynamics of NovoLog® has not been studied.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Standard 2-year carcinogenicity studies in animals have not been performed to evaluate the carcinogenic potential of NovoLog®. In 52-week studies, Sprague-Dawley rats were dosed subcutaneously with NovoLog® at 10, 50, and 200 U/kg/day (approximately 2, 8, and 32 times the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area, respectively). At a dose of 200 U/kg/day, NovoLog® increased the incidence of mammary gland tumors in females when compared to untreated controls. The incidence of mammary tumors for NovoLog® was not significantly different than for regular human insulin. The relevance of these findings to humans is not known. NovoLog® was not genotoxic in the following tests: Ames test, mouse lymphoma cell forward gene mutation test, human peripheral blood lymphocyte chromosome aberration test, *in vivo* micronucleus test in mice, and in *ex vivo* UDS test in rat liver hepatocytes. In fertility studies in male and female rats, at subcutaneous doses up to 200 U/kg/day (approximately 32 times the human subcutaneous dose, based on U/body surface area), no direct adverse effects on male and female fertility, or general reproductive performance of animals was observed.

13.2 Animal Toxicology and/or Pharmacology

In standard biological assays in mice and rabbits, one unit of NovoLog® has the same glucose-lowering effect as one unit of regular human insulin. In humans, the effect of NovoLog® is more rapid in onset and of shorter duration, compared to regular human insulin, due to its faster absorption after subcutaneous injection (see *Section 12 CLINICAL PHARMACOLOGY* Figure 2 and Figure 4).

14 CLINICAL STUDIES

14.1 Subcutaneous Daily Injections

Two six-month, open-label, active-controlled studies were conducted to compare the safety and efficacy of NovoLog® to Novolin® R in adult patients with type 1 diabetes. Because the two study designs and results were similar, data are shown for only one study (see Table 3). NovoLog® was administered by subcutaneous injection immediately prior to meals and regular human insulin was administered by subcutaneous injection 30 minutes before meals. NPH insulin was administered as the basal insulin in either single or divided daily doses. Changes in HbA_{1c} and the incidence rates of severe hypoglycemia (as determined from the number of events requiring intervention from a third party) were comparable for the two treatment regimens in this study (Table 3) as well as in the other clinical studies that are cited in this section. Diabetic ketoacidosis was not reported in any of the adult studies in either treatment group.

Table 3. Subcutaneous NovoLog® Administration in Type 1 Diabetes (24 weeks; n=882)

	NovoLog® + NPH	Novolin® R + NPH
N	596	286
Baseline HbA_{1c} (%)*	7.9 ± 1.1	8.0 ± 1.2
Change from Baseline HbA_{1c} (%)	-0.1 ± 0.8	0.0 ± 0.8
Treatment Difference in HbA_{1c}, Mean (95% confidence interval)	-0.2 (-0.3, -0.1)	
Baseline insulin dose (IU/kg/24 hours)*	0.7 ± 0.2	0.7 ± 0.2
End-of-Study insulin dose (IU/kg/24 hours)*	0.7 ± 0.2	0.7 ± 0.2
Patients with severe hypoglycemia (n, %)**	104 (17%)	54 (19%)
Baseline body weight (kg)* Weight Change from baseline (kg)*	75.3 ± 14.5 0.5 ± 3.3	75.9 ± 13.1 0.9 ± 2.9

*Values are Mean ± SD

**Severe hypoglycemia refers to hypoglycemia associated with central nervous system symptoms and requiring the intervention of another person or hospitalization.

A 24-week, parallel-group study of children and adolescents with type 1 diabetes (n = 283) aged 6 to 18 years compared two subcutaneous multiple-dose treatment regimens: NovoLog® (n = 187) or Novolin® R (n = 96). NPH insulin was administered as the basal insulin. NovoLog® achieved glycemic control comparable to Novolin® R, as measured by change in HbA_{1c} (Table 4) and both treatment groups had a comparable incidence of hypoglycemia. Subcutaneous administration of NovoLog® and regular human insulin have also been compared in children with type 1 diabetes (n=26) aged 2 to 6 years with similar effects on HbA_{1c} and hypoglycemia.

Table 4. Pediatric Subcutaneous Administration of NovoLog® in Type 1 Diabetes (24 weeks; n=283)

	NovoLog® + NPH	Novolin® R + NPH
N	187	96
Baseline HbA_{1c} (%)*	8.3 ± 1.2	8.3 ± 1.3
Change from Baseline HbA_{1c} (%)	0.1 ± 1.0	0.1 ± 1.1
Treatment Difference in HbA_{1c}, Mean (95% confidence interval)	0.1 (-0.5, 0.1)	
Baseline insulin dose (IU/kg/24 hours)*	0.4 ± 0.2	0.6 ± 0.2
End-of-Study insulin dose (IU/kg/24 hours)*	0.4 ± 0.2	0.7 ± 0.2
Patients with severe hypoglycemia (n, %)**	11 (6%)	9 (9%)
Diabetic ketoacidosis (n, %)	10 (5%)	2 (2%)
Baseline body weight (kg)* Weight Change from baseline (kg)*	50.6 ± 19.6 2.7 ± 3.5	48.7 ± 15.8 2.4 ± 2.6

*Values are Mean ± SD

**Severe hypoglycemia refers to hypoglycemia associated with central nervous system symptoms and requiring the intervention of another person or hospitalization.

One six-month, open-label, active-controlled study was conducted to compare the safety and efficacy of NovoLog® to Novolin® R in patients with type 2 diabetes (Table 5). NovoLog® was administered by subcutaneous injection immediately prior to meals and regular human insulin was administered by subcutaneous injection 30 minutes before meals. NPH insulin was administered as the basal insulin in either single or divided daily doses. Changes in HbA_{1c} and the rates of severe hypoglycemia (as determined from the number of events requiring intervention from a third party) were comparable for the two treatment regimens.

Table 5. Subcutaneous NovoLog® Administration in Type 2 Diabetes (6 months; n=176)

	NovoLog® + NPH	Novolin® R + NPH
N	90	86
Baseline HbA_{1c} (%)*	8.1 ± 1.2	7.8 ± 1.1
Change from Baseline HbA_{1c} (%)	-0.3 ± 1.0	-0.1 ± 0.8
Treatment Difference in HbA_{1c}, Mean (95% confidence interval)	- 0.1 (-0.4, -0.1)	
Baseline insulin dose (IU/kg/24 hours)*	0.6 ± 0.3	0.6 ± 0.3
End-of-Study insulin dose (IU/kg/24 hours)*	0.7 ± 0.3	0.7 ± 0.3
Patients with severe hypoglycemia (n, %)**	9 (10%)	5 (8%)
Baseline body weight (kg)* Weight Change from baseline (kg)*	88.4 ± 13.3 1.2 ± 3.0	85.8 ± 14.8 0.4 ± 3.1

*Values are Mean ± SD

**Severe hypoglycemia refers to hypoglycemia associated with central nervous system symptoms and requiring the intervention of another person or hospitalization.

14.2 Continuous Subcutaneous Insulin Infusion (CSII) by External Pump

Two open-label, parallel design studies (6 weeks [n=29] and 16 weeks [n=118]) compared NovoLog® to buffered regular human insulin (Velosulin) in adults with type 1 diabetes receiving a subcutaneous infusion with an external insulin pump. The two treatment regimens had comparable changes in HbA_{1c} and rates of severe hypoglycemia.

Table 6. Adult Insulin Pump Study in Type 1 Diabetes (16 weeks; n=118)

	NovoLog®	Buffered human insulin
N	59	59
Baseline HbA_{1c} (%)*	7.3 ± 0.7	7.5 ± 0.8
Change from Baseline HbA_{1c} (%)	0.0 ± 0.5	0.2 ± 0.6
Treatment Difference in HbA_{1c}, Mean (95% confidence interval)	0.3 (-0.1, 0.4)	
Baseline insulin dose (IU/kg/24 hours)*	0.7 ± 0.8	0.6 ± 0.2
End-of-Study insulin dose (IU/kg/24 hours)*	0.7 ± 0.7	0.6 ± 0.2
Patients with severe hypoglycemia (n, %)**	1 (2%)	2 (3%)
Baseline body weight (kg)* Weight Change from baseline (kg)*	77.4 ± 16.1 0.1 ± 3.5	74.8 ± 13.8 -0.0 ± 1.7

*Values are Mean ± SD

**Severe hypoglycemia refers to hypoglycemia associated with central nervous system symptoms and requiring the intervention of another person or hospitalization.

A randomized, 16-week, open-label, parallel design study of children and adolescents with type 1 diabetes (n=298) aged 4-18 years compared two subcutaneous infusion regimens administered via an external insulin pump: NovoLog® (n=198) or insulin lispro (n=100). These two treatments resulted in comparable changes from baseline in HbA_{1c} and comparable rates of hypoglycemia after 16 weeks of treatment (see Table 7).

Table 7. Pediatric Insulin Pump Study in Type 1 Diabetes (16 weeks; n=298)

	NovoLog®	Lispro
N	198	100
Baseline HbA_{1c} (%)*	8.0 ± 0.9	8.2 ± 0.8
Change from Baseline HbA_{1c} (%)	-0.1 ± 0.8	-0.1 ± 0.7
Treatment Difference in HbA_{1c}, Mean (95% confidence interval)	-0.1 (-0.3, 0.1)	
Baseline insulin dose (IU/kg/24 hours)*	0.9 ± 0.3	0.9 ± 0.3
End-of-Study insulin dose (IU/kg/24 hours)*	0.9 ± 0.2	0.9 ± 0.2
Patients with severe hypoglycemia (n, %)**	19 (10%)	8 (8%)
Diabetic ketoacidosis (n, %)	1 (0.5%)	0 (0)
Baseline body weight (kg)* Weight Change from baseline (kg)*	54.1 ± 19.7 1.8 ± 2.1	55.5 ± 19.0 1.6 ± 2.1

*Values are Mean ± SD

**Severe hypoglycemia refers to hypoglycemia associated with central nervous system symptoms and requiring the intervention of another person or hospitalization.

An open-label, 16-week parallel design trial compared pre-prandial NovoLog® injection in conjunction with NPH injections to NovoLog® administered by continuous subcutaneous infusion in 127 adults with type 2 diabetes. The two treatment groups had similar reductions in HbA_{1c} and rates of severe hypoglycemia (Table 8) [*see Indications and Usage (1), Dosage and Administration (2), Warnings and Precautions (5) and How Supplied/Storage and Handling (16.2)*].

Table 8. Pump Therapy in Type 2 Diabetes (16 weeks; n=127)

	NovoLog® pump	NovoLog® + NPH
N	66	61
Baseline HbA_{1c} (%)*	8.2 ± 1.4	8.0 ± 1.1
Change from Baseline HbA_{1c} (%)	-0.6 ± 1.1	-0.5 ± 0.9
Treatment Difference in HbA_{1c}, Mean (95% confidence interval)	0.1 (0.4, 0.3)	
Baseline insulin dose (IU/kg/24 hours)*	0.7 ± 0.3	0.8 ± 0.5
End-of-Study insulin dose (IU/kg/24 hours)*	0.9 ± 0.4	0.9 ± 0.5
Baseline body weight (kg)* Weight Change from baseline (kg)*	96.4 ± 17.0 1.7 ± 3.7	96.9 ± 17.9 0.7 ± 4.1

*Values are Mean ± SD

14.3 Intravenous Administration of NovoLog®

See Section 12.2 CLINICAL PHARMACOLOGY/Pharmacodynamics.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

NovoLog® is available in the following package sizes: each presentation containing 100 Units of insulin aspart per mL (U-100).

10 mL vials	NDC 0169-7501-11
3 mL PenFill® cartridges*	NDC 0169-3303-12
3 mL NovoLog® FlexPen®	NDC 0169-6339-10

*NovoLog® PenFill® cartridges are designed for use with Novo Nordisk 3 mL PenFill® cartridge compatible insulin delivery devices (with or without the addition of a NovoPen® 3 PenMate®) with NovoFine® disposable needles.

16.2 Recommended Storage

Unused NovoLog® should be stored in a refrigerator between 2° and 8°C (36° to 46°F). Do not store in the freezer or directly adjacent to the refrigerator cooling element. **Do not freeze NovoLog® and do not use NovoLog® if it has been frozen.** NovoLog® should not be drawn into a syringe and stored for later use.

Vials: After initial use a vial may be kept at temperatures below 30°C (86°F) for up to 28 days, but should not be exposed to excessive heat or sunlight. Opened vials may be refrigerated.

Unpunctured vials can be used until the expiration date printed on the label if they are stored in a refrigerator. Keep unused vials in the carton so they will stay clean and protected from light.

PenFill® cartridges or NovoLog® FlexPen®:

Once a cartridge or a NovoLog® FlexPen® is punctured, it should be kept at temperatures below 30°C (86°F) for up to 28 days, but should not be exposed to excessive heat or sunlight. A NovoLog® FlexPen® or cartridge in use must NOT be stored in the refrigerator. Keep the NovoLog® FlexPen® and all PenFill® cartridges away from direct heat and sunlight. Unpunctured NovoLog® FlexPen® and PenFill® cartridges can be used until the expiration date printed on the label if they are stored in a refrigerator. Keep unused NovoLog® FlexPen® and PenFill® cartridges in the carton so they will stay clean and protected from light.

Always remove the needle after each injection and store the 3 mL PenFill® cartridge delivery device or NovoLog® FlexPen® without a needle attached. This prevents contamination and/or infection, or leakage of insulin, and will ensure accurate dosing. Always use a new needle for each injection to prevent contamination.

Pump:

NovoLog® in the pump reservoir should be discarded after at least every 6 days of use or after exposure to temperatures that exceed 37°C (98.6°F). The infusion set and the infusion set insertion site should be changed at least every 3 days.

Summary of Storage Conditions:

The storage conditions are summarized in the following table:

Table 9. Storage conditions for vial, PenFill® cartridges and NovoLog® FlexPen®

NovoLog® presentation	**Not in-use (unopened)** Room Temperature (below 30°C)	**Not in-use (unopened)** Refrigerated	**In-use (opened)** Room Temperature (below 30°C)
10 mL vial	28 days	Until expiration date	28 days (refrigerated/room temperature)
3 mL PenFill® cartridges	28 days	Until expiration date	28 days (Do not refrigerate)
3 mL NovoLog® FlexPen®	28 days	Until expiration date	28 days (Do not refrigerate)

Storage of Diluted NovoLog®

NovoLog® diluted with Insulin Diluting Medium for NovoLog® to a concentration equivalent to U-10 or equivalent to U-50 may remain in patient use at temperatures below 30°C (86°F) for 28 days.

Storage of NovoLog® in Infusion Fluids

Infusion bags prepared as indicated under *Dosage and Administration (2)* are stable at room temperature for 24 hours. Some insulin will be initially adsorbed to the material of the infusion bag.

17 PATIENT COUNSELING INFORMATION

[*See FDA-Approved Patient Labeling (17.3)*]

17.1 Physician Instructions

Maintenance of normal or near-normal glucose control is a treatment goal in diabetes mellitus and has been associated with a reduction in diabetic complications. Patients should be informed about potential risks and benefits of NovoLog® therapy including the possible adverse reactions. Patients should also be offered continued education and advice on insulin therapies, injection technique, life-style management, regular glucose monitoring, periodic glycosylated hemoglobin testing, recognition and management of hypo- and hyperglycemia, adherence to meal planning, complications of insulin therapy, timing of dose, instruction in the use of injection or subcutaneous infusion devices, and proper storage of insulin. Patients should be informed that frequent, patient-performed blood glucose measurements are needed to achieve optimal glycemic control and avoid both hyper- and hypoglycemia.

The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. This may present a risk in situations where these abilities are especially important, such as driving or operating other machinery. Patients who have frequent hypoglycemia or reduced or absent warning signs of hypoglycemia should be advised to use caution when driving or operating machinery.

Accidental substitutions between NovoLog® and other insulin products have been reported. Patients should be instructed to always carefully check that they are administering the appropriate insulin to avoid medication errors between NovoLog® and any other insulin. **The written prescription for NovoLog® should be written clearly, to avoid confusion with other insulin products, for example, NovoLog® Mix 70/30.**

17.2 Patients Using Pumps

Patients using external pump infusion therapy should be trained in intensive insulin therapy with multiple injections and in the function of their pump and pump accessories.

The following insulin pumps† have been used in NovoLog® clinical or *in vitro* studies conducted by Novo Nordisk, the manufacturer of NovoLog®:

- Medtronic Paradigm® 512 and 712
- MiniMed 508
- Disetronic® D-TRON® and H-TRON®

Before using another insulin pump with NovoLog®, read the pump label to make sure the pump has been evaluated with NovoLog®.

NovoLog® is recommended for use in any reservoir and infusion sets that are compatible with insulin and the specific pump. Please see recommended reservoir and infusion sets in the pump manual.

To avoid insulin degradation, infusion set occlusion, and loss of the preservative (metacresol), insulin in the reservoir should be replaced at least every 6 days; infusion sets and infusion set insertion sites should be changed at least every 3 days.

Insulin exposed to temperatures higher than 37°C (98.6°F) should be discarded. The temperature of the insulin may exceed ambient temperature when the pump housing, cover, tubing, or sport case is exposed to sunlight or radiant heat. Infusion sites that are erythematous, pruritic, or thickened should be reported to medical personnel, and a new site selected because continued infusion may increase the skin reaction and/or alter the absorption of NovoLog®. Pump or infusion set malfunctions or insulin degradation can lead to hyperglycemia and ketosis in a short time because of the small subcutaneous depot of insulin. This is especially pertinent for rapid-acting insulin analogs that are more rapidly absorbed through skin and have shorter duration of action. These differences are particularly relevant when patients are switched from multiple injection therapy. Prompt identification and correction of the cause of hyperglycemia or ketosis is necessary. Problems include pump malfunction, infusion set occlusion, leakage, disconnection or kinking, and degraded insulin. Less commonly, hypoglycemia from pump malfunction may occur. If these problems cannot be promptly corrected, patients should resume therapy with subcutaneous insulin injection and contact their physician [*see Dosage and Administration (2), Warnings and Precautions (5) and How Supplied/Storage and Handling (16.2)*].

17.3 FDA Approved Patient Labeling

See separate leaflet.

Rx only

Date of Issue: June 2011
Version: 19

Novo Nordisk®, NovoLog®, NovoPen® 3, PenFill®, Novolin®, FlexPen®, PenMate® and NovoFine® are registered trademarks of Novo Nordisk A/S.

NovoLog® is covered by US Patent Nos. 5,618,913; 5,866,538, and other patents pending. FlexPen® is covered by US Patent Nos. 6,582,404; 6,004,297; 6,235,004, and other patents pending. PenFill® is covered by US Patent No. 5,693,027.

†The brands listed are the registered trademarks of their respective owners and are not trademarks of Novo Nordisk A/S.

Manufactured by:
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novo nordisk®

Patient Information

NovoLog® (NŌ-vō-log)
(insulin aspart [rDNA origin] Injection)

Important:

Know your insulin. Do not change the type of insulin you use unless told to do so by your healthcare provider. The amount of insulin you take as well as the best time for you to take your insulin may need to change if you take a different type of insulin.

Make sure you know the type and strength of insulin prescribed for you.

Read the Patient Information that comes with NovoLog® before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your diabetes or your treatment. Make sure you know how to manage your diabetes. Ask your healthcare provider if you have any questions about managing your diabetes.

What is NovoLog®?

NovoLog® is a man-made insulin that is used to control high blood sugar in adults and children with diabetes mellitus.

Who should not use NovoLog®?

Do not take NovoLog® if:

- Your blood sugar is too low (hypoglycemia).
- You are allergic to anything in NovoLog®. See the end of this leaflet for a complete list of ingredients in NovoLog®. Check with your healthcare provider if you are not sure.

Tell your healthcare provider:

- **about all of your medical conditions**. Medical conditions can affect your insulin needs and your dose of NovoLog®.
- **if you are pregnant or breastfeeding**. You and your healthcare provider should talk about the best way to manage your diabetes while you are pregnant or breastfeeding. NovoLog® has not been studied in nursing women.
- **about all medicines you take**, including prescriptions and non-prescription medicines, vitamins and herbal supplements. Your NovoLog® dose may change if you take other medicines.

Know the medicines you take. Keep a list of your medicines with you to show your healthcare providers when you get a new medicine.

How should I take NovoLog®?

Only use NovoLog® if it appears clear and colorless. There may be air bubbles. This is normal. If it looks cloudy, thickened, or colored, or if it contains solid particles do not use it and call Novo Nordisk at 1-800-727-6500.

NovoLog® comes in:

- 10 mL vials (small bottles) for use with syringe
- 3 mL PenFill® cartridges for use with the Novo Nordisk 3 mL PenFill® cartridge compatible insulin delivery devices and NovoFine® disposable needles. The cartridge delivery device can be used with a NovoPen® 3 PenMate®
- 3 mL NovoLog® FlexPen®

Read the instructions for use that come with your NovoLog® product. Talk to your healthcare provider if you have any questions. Your healthcare provider should show you how to inject NovoLog® before you start taking it.

- **Take NovoLog® exactly as prescribed**. You should eat a meal within 5 to 10 minutes after using NovoLog® to avoid low blood sugar.
- **NovoLog® is a fast-acting insulin**. The effects of NovoLog® start working 10 to 20 minutes after injection or bolus pump infusion.
- **Do not inject NovoLog® if you do not plan to eat right after your injection or bolus pump infusion**.
- The greatest blood sugar lowering effect is between 1 and 3 hours after the injection or infusion. This blood sugar lowering lasts for 3 to 5 hours.
- **While using NovoLog® you may have to change** your total dose of insulin, your dose of longer-acting insulin, or the number of injections of longer-acting insulin you use. Pump users given NovoLog® may need to change the amount of total insulin given as a basal infusion.
- **Do not mix NovoLog®**:
  - with any other insulins when used in a pump
  - with any insulins other than NPH when used with injections by syringe

If your healthcare provider recommends diluting NovoLog®, follow your healthcare provider's instructions exactly so that you know:

- How to make NovoLog® more dilute (that is, a smaller number of units of NovoLog® for a given amount of liquid) and
- How to use this more dilute form of NovoLog®. **Do not use dilute insulin in a pump**.
- **Inject NovoLog® into the skin of your stomach area, upper arms, buttocks or upper legs**. NovoLog® may affect your blood sugar levels sooner if you inject it into the skin of your stomach area. **Never inject NovoLog® into a vein or into a muscle**.
- **Change (rotate) your injection site within the chosen area (for example, stomach or upper arm) with each dose. Do not inject into the exact same spot for each injection**.
- **If you take too much NovoLog®, your blood sugar may fall low (hypoglycemia)**. You can treat mild low blood sugar (hypoglycemia) by drinking or eating something sugary right away (fruit juice, sugar candies, or glucose tablets). It is important to treat low blood sugar (hypoglycemia) right away because it could get worse and you could pass out (become unconscious). If you pass out you will need help from another person or emergency medical services right away, and will need treatment with a glucagon injection or treatment at a hospital. See "What are the possible side effects of NovoLog®?" for more information on low blood sugar (hypoglycemia).
- **If you forget to take your dose of NovoLog®, your blood sugar may go too high (hyperglycemia)**. If high blood sugar (hyperglycemia) is not treated it can lead to serious problems, like loss of consciousness (passing out), coma or even death. Follow your healthcare provider's instructions for treating high blood sugar. Know your symptoms of high blood sugar which may include:
  - increased thirst
  - frequent urination
  - loss of appetite
  - high amounts of sugar and ketones in your urine
  - nausea, vomiting (throwing up) or stomach pain
  - fruity smell on the breath
  - drowsiness
  - a hard time breathing
- **Check your blood sugar levels.** Ask your healthcare provider what your blood sugars should be and when you should check your blood sugar levels.

Your insulin dosage may need to change because of:

- illness
- stress
- change in physical activity or exercise
- change in diet
- other medicines you take

What should I avoid while using NovoLog®?

- **Alcohol.** Alcohol, including beer and wine, may affect your blood sugar when you take NovoLog®.
- **Driving and operating machinery.** You may have difficulty concentrating or reacting if you have low blood sugar (hypoglycemia). Be careful when you drive a car or operate machinery. Ask your healthcare provider if it is alright to drive if you often have:
  - low blood sugar
  - decreased or no warning signs of low blood sugar

What are the possible side effects of NovoLog®?

- **Low blood sugar (hypoglycemia).** Symptoms of low blood sugar may include:
  - sweating
  - trouble concentrating or confusion
  - dizziness or lightheadedness
  - shakiness
  - fast heart beat
  - anxiety, irritability or mood changes
  - headache
  - blurred vision
  - hunger
  - slurred speech
  - tingling of lips and tongue

  Severe low blood sugar can cause unconsciousness (passing out), seizures, and death. Know your symptoms of low blood sugar. Follow your healthcare provider's instructions for treating low blood sugar. Talk to your healthcare provider if low blood sugar is a problem for you.
- **Serious allergic reaction (whole body reaction)**. **Get medical help right away, if you develop** a rash over your whole body, have trouble breathing, a fast heartbeat, or sweating.
- **Reactions at the injection site (local allergic reaction)**. You may get redness, swelling, and itching at the injection site. If you keep having skin reactions or they are serious talk to your healthcare provider. You may need to stop using NovoLog® and use a different insulin. Do not inject insulin into skin that is red, swollen, or itchy.
- **Skin thickens or pits at the injection site (lipodystrophy)**. Change (rotate) where you inject your insulin to help to prevent these skin changes from happening. Do not inject insulin into this type of skin.
- **Swelling of your hands and feet**
- **Vision changes**
- **Low potassium in your blood (hypokalemia)**
- **Weight gain**

These are not all of the possible side effects from NovoLog®.

Ask your healthcare provider or pharmacist for more information.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store NovoLog®?

All Unopened NovoLog®:

- **Keep all unopened NovoLog® in the refrigerator between 36° to 46°F (2° to 8°C).**
- Do not freeze. Do not use NovoLog® if it has been frozen.
- Keep unopened NovoLog® in the carton to protect from light.

NovoLog® in use:

- **Vials**
  - Keep in the refrigerator or at room temperature below 86°F (30°C) for up to 28 days.
  - Keep vials away from direct heat or light.
  - Throw away an opened vial after 28 days of use, even if there is insulin left in the vial.
  - Do not draw up NovoLog® into a syringe and store for later use.
  - Unopened vials can be used until the expiration date on the NovoLog® label, if the medicine has been stored in a refrigerator.
- **PenFill® Cartridges or NovoLog® FlexPen®**
  - Keep at room temperature below 86°F (30°C) for up to 28 days.
  - Do not store a PenFill® cartridge or NovoLog® FlexPen® that you are using in the refrigerator.
  - Keep PenFill® cartridges and NovoLog® FlexPen® away from direct heat or light.
  - Throw away a used PenFill® cartridge or NovoLog® FlexPen® after 28 days, even if there is insulin left in the cartridge or syringe.
- **NovoLog® in the pump reservoir and the complete external pump infusion set**
  - The infusion set and the infusion site should be changed **at least every 3 days**. The insulin in the reservoir should be changed **at least every 6 days** even if you have not used all of the insulin. Change the infusion set and the infusion site more often than every 3 days if you have high blood sugar (hyperglycemia), the pump alarm sounds, or the insulin flow is blocked (occlusion).

General advice about NovoLog®

Medicines are sometimes prescribed for conditions that are not mentioned in the patient leaflet. Do not use NovoLog® for a condition for which it was not prescribed. Do not give NovoLog® to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about NovoLog®. If you would like more information about NovoLog® or diabetes, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about NovoLog® that is written for healthcare professionals. Call 1-800-727-6500 or visit www.novonordisk-us.com for more information.

Helpful information for people with diabetes is published by the American Diabetes Association, 1701 N Beauregard Street, Alexandria, VA 22311 and on www.diabetes.org.

NovoLog® ingredients include:

- insulin aspart
- glycerin
- metacresol
- disodium hydrogen phosphate dihydrate
- water for injection
- zinc
- phenol
- sodium chloride

All NovoLog® vials, PenFill® cartridges and NovoLog® FlexPen® are latex free.

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Novo Nordisk®, NovoLog®, PenFill®, FlexPen®, NovoPen®, NovoFine®, and PenMate® are registered trademarks of Novo Nordisk A/S.

NovoLog® is covered by US Patent Nos. 5,618,913, 5,866,538, and other patents pending.

FlexPen® is covered by US Patent Nos. 6,582,404, 6,004,297, 6,235,004, and other patents pending.

PenFill® is covered by US Patent No. 5,693,027.

Manufactured by:
Novo Nordisk A/S
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Patient Instructions for Use

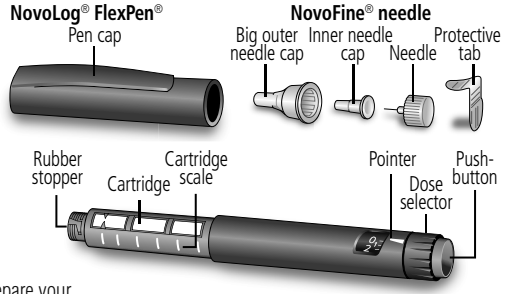
NovoLog® FlexPen®

Introduction

Please read the following instructions carefully before using your NovoLog® FlexPen®.

NovoLog® FlexPen® is a disposable dial-a-dose insulin pen. You can select doses from 1 to 60 units in increments of 1 unit. NovoLog® FlexPen® is designed to be used with NovoFine® needles.

⚠ NovoLog® FlexPen® should not be used by people who are blind or have severe visual problems without the help of a person who has good eyesight and who is trained to use the NovoLog® FlexPen® the right way.



Getting ready

Make sure you have the following items:

- NovoLog® FlexPen®
- New NovoFine® needle
- Alcohol swab

Preparing Your NovoLog® FlexPen®

Wash your hands with soap and water. Before you start to prepare your injection, check the label to make sure that you are taking the right type of insulin. This is especially important if you take more than 1 type of insulin. NovoLog® should look clear.

A. Pull off the pen cap (see diagram A).

Wipe the rubber stopper with an alcohol swab.

B. Attaching the needle

Remove the protective tab from a disposable needle.

Screw the needle tightly onto your FlexPen®. It is important that the needle is put on straight (see diagram B).

Never place a disposable needle on your NovoLog® FlexPen® until you are ready to take your injection.

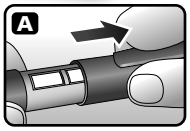
C. Pull off the big outer needle cap (see diagram C).

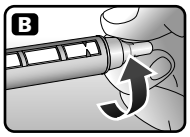
D. Pull off the inner needle cap and dispose of it (see diagram D).

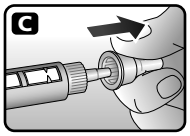
⚠ Always use a new needle for each injection to help ensure sterility and prevent blocked needles.

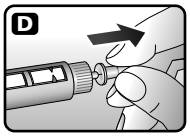
⚠ Be careful not to bend or damage the needle before use.

⚠ To reduce the risk of unexpected needle sticks, never put the inner needle cap back on the needle.









Giving the airshot before each injection

Before each injection small amounts of air may collect in the cartridge during normal use. To avoid injecting air and to ensure proper dosing:

E. Turn the dose selector to select 2 units (see diagram E).

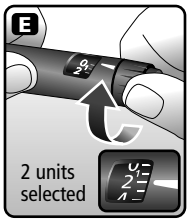
F. Hold your NovoLog® FlexPen® with the needle pointing up. Tap the cartridge gently with your finger a few times to make any air bubbles collect at the top of the cartridge (see diagram F).

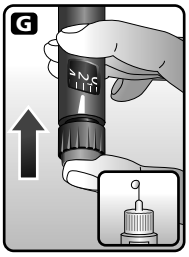
G. Keep the needle pointing upwards, press the push-button all the way in (see diagram G). The dose selector returns to 0.

A drop of insulin should appear at the needle tip. If not, change the needle and repeat the procedure no more than 6 times.

If you do not see a drop of insulin after 6 times, do not use the NovoLog® FlexPen® and contact Novo Nordisk at 1-800-727-6500.

A small air bubble may remain at the needle tip, but it will not be injected.





Selecting your dose

Check and make sure that the dose selector is set at 0.

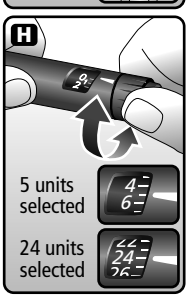
H. Turn the dose selector to the number of units you need to inject. The pointer should line up with your dose.

The dose can be corrected either up or down by turning the dose selector in either direction until the correct dose lines up with the pointer (see diagram H). When turning the dose selector, be careful not to press the push-button as insulin will come out.

You cannot select a dose larger than the number of units left in the cartridge.

You will hear a click for every single unit dialed. Do not set the dose by counting the number of clicks you hear.

⚠ Do not use the cartridge scale printed on the cartridge to measure your dose of insulin.



Giving the injection

Do the injection exactly as shown to you by your healthcare provider. Your healthcare provider should tell you if you need to pinch the skin before injecting.

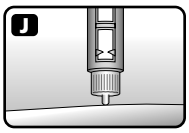
I. Insert the needle into your skin.

Inject the dose by pressing the push-button all the way in until the 0 lines up with the pointer (see diagram I). Be careful only to push the button when injecting.

Turning the dose selector will not inject insulin.

J. Keep the needle in the skin for at least 6 seconds, and keep the push-button pressed all the way in until the needle has been pulled out from the skin (see diagram J). This will make sure that the full dose has been given.

You may see a drop of NovoLog® at the needle tip. This is normal and has no effect on the dose you just received. If blood appears after you take the needle out of your skin, press the injection site lightly with a finger. **Do not rub the area.**



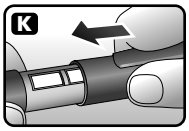
After the injection

Do not recap the needle. Recapping can lead to a needle stick injury. Remove the needle from the NovoLog® FlexPen® after each injection. This helps to prevent infection, leakage of insulin, and will help to make sure you inject the right dose of insulin.

⚠ Put the needle and any empty NovoLog® FlexPen® or any used NovoLog® FlexPen® still containing insulin in a sharps container or some type of hard plastic or metal container with a screw top such as a detergent bottle or empty coffee can. These containers should be sealed and thrown away the right way. Check with your healthcare provider about the right way to throw away used syringes and needles. There may be local or state laws about how to throw away used needles and syringes. Do not throw away used needles and syringes in household trash or recycling bins.

The NovoLog® FlexPen® prevents the cartridge from being completely emptied. It is designed to deliver 300 units.

K. Put the pen cap on the NovoLog® FlexPen® and store the NovoLog® FlexPen® without the needle attached (see diagram K).

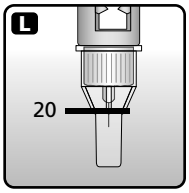


Function Check

L. If your NovoLog® FlexPen® is not working the right way, follow the steps below:

- Screw on a new NovoFine® needle.
- Remove the big outer needle cap and the inner needle cap.
- Do an airshot as described in "Giving the airshot before each injection".
- Put the big outer needle cap onto the needle. Do not put on the inner needle cap.
- Turn the dose selector so the dose indicator window shows 20 units.
- Hold the NovoLog® FlexPen® so the needle is pointing down.
- Press the push-button all the way in.

The insulin should fill the lower part of the big outer needle cap (see diagram L). If the NovoLog® FlexPen® has released too much or too little insulin, do the function check again. If the same problem happens again, do not use your NovoLog® FlexPen® and contact Novo Nordisk at 1-800-727-6500.



Maintenance

Your FlexPen® is designed to work accurately and safely. It must be handled with care. Avoid dropping your FlexPen® as it may damage it. If you are concerned that your FlexPen® is damaged, use a new one. You can clean the outside of your FlexPen® by wiping it with a damp cloth. Do not soak or wash your FlexPen® as it may damage it. Do not refill your FlexPen®.

⚠ Remove the needle from the NovoLog® FlexPen® after each injection. This helps to ensure sterility, prevent leakage of insulin, and will help to make sure you inject the right dose of insulin for future injections.

⚠ Be careful when handling used needles to avoid needle sticks and transfer of infectious diseases.

⚠ Keep your NovoLog® FlexPen® and needles out of the reach of children.

⚠ Use NovoLog® FlexPen® as directed to treat your diabetes.

⚠ Needles and NovoLog® FlexPen® must not be shared. Always use a new needle for each injection.

⚠ Novo Nordisk is not responsible for harm due to using this insulin pen with products not recommended by Novo Nordisk.

⚠ As a precautionary measure, always carry a spare insulin delivery device in case your NovoLog® FlexPen® is lost or damaged.

⚠ Remember to keep the disposable NovoLog® FlexPen® with you. Do not leave it in a car or other location where it can get too hot or too cold.

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